The Potentiation of Radiation Effects With 5-Fluoro-uracil

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• **A preliminary study of the response of various inoperable malignant diseases to simultaneously administered 5-fluoro-uracil and orthovolt x-ray was performed. The 5-fluoro-uracil was given intravenously at a relatively nontoxic dosage level. The x-ray tumor dose was limited to 2,000 roentgens in every patient.**

Pronounced and rapid tumor regression occurred in 12 of 18 evaluable patients. Significant objective response was obtained in each of eight patients with epidermoid carcinoma of the lung.

Toxicity occurred in half of the patients, manifested by pharyngitis, esophagitis, proctitis, leukopenia and thrombocytopenia.

THE ANTI-CANCER EFFECTS of the substituted purine and pyrimidine compounds have been thoroughly evaluated by many investigators. Synthesized several years ago,[3] 5-fluoro-uracil, a halogenated pyrimidine, has had extensive trial in a variety of malignant tumors.[1,2,4] Curreri and coworkers[2] obtained objective improvement in patients with carcinoma of the breast, ovary, cervix, colon and rectum, and hepatoma treated with toxic doses of 5-fluoro-uracil given intravenously. They observed no beneficial effect in patients with carcinoma of the lung, stomach, pancreas, malignant melanoma or hypernephroma. Toxic effects of the compound were nausea, vomiting, stomatitis, diarrhea and bone-marrow depression and, when severe, included gastrointestinal ulceration and hemorrhage, ileus, shock, bilateral pneumonia, agranulocytosis and death.

In late 1958, one of the authors (B.H.), who was treating a patient with squamous cell carcinoma with 5-fluoro-uracil and local x-ray simultaneously, observed a degree of tumor response that suggested unusual radiosensitivity for malignant lesions of this type. In an attempt to evaluate the suspicion of possible synergism of these two modes of therapy, we initiated a preliminary study employing these agents concomitantly in patients with inoperable malignant disease. Trying to avoid severe toxicity, we used a smaller total dose of 5-fluoro-uracil than other investigators had reported.

THE SCHEDULE OF TREATMENT (Chart 1)

5-Fluoro-uracil was administered by slow intravenous drip (3 to 4 hours in 200 to 500 cc. of normal saline solution on the following schedule:

Days 1 through 4: 15 mg. per kg. of body weight (in no case more than 1,000 mg. a day).

Day 5 and twice weekly thereafter: 7.5 mg. per kg. (in no case more than 500 mg. a day).

The irradiation was administered at 250 kilovolts (half value layer 3 mm. of copper) in daily tumor doses of 100 to 200 roentgens, five days a week, to a total tumor dose of 2,000 r. The usual course of combined therapy required two weeks, the patient receiving approximately 90 mg. of 5-fluoro-uracil per kilogram of body weight.

The radiation dosage of 2,000 r. was chosen for several reasons. Several experienced radiotherapists stated that the majority of tumors of the type we planned to treat would not respond significantly to this dose level; this dose of radiation could be given over several areas in the same patient without undue side effects; and, finally, an increase in tumor sensitivity of a lesser degree would be of no practical value.

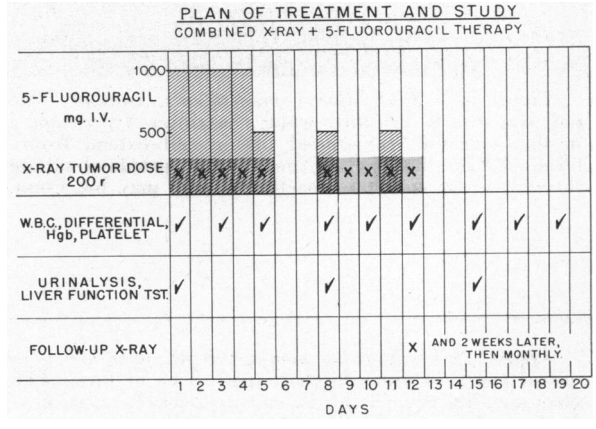

Chart 1

From the Departments of Medicine and Radiology, Veterans Administration Hospital, San Francisco.

5-Fluoro-uracil was generously supplied by Hoffman-LaRoche, Inc., Nutley, New Jersey.

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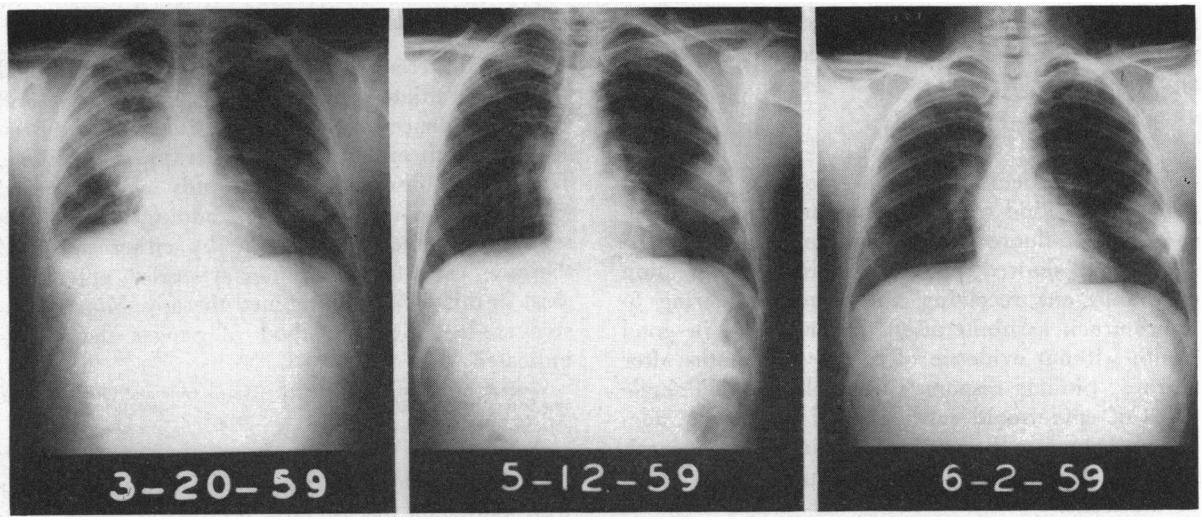

Figure 1.—Embryonal cell carcinoma, with metastastic lesions in both lung fields. *Left,* before treatment. *Center,* two weeks after treatment with 5-fluoro-uracil. X-ray (2,000 r.) was administered concurrently to the lesion in the right lung. The mass in the left lung was exposed to 5-fluoro-uracil alone. *Right,* two weeks after treatment of left lung mass with x-ray (2,000 r.) alone.

Patients were selected by the following criteria:

1. The disease must be biopsy-proven, inoperable, and measurable objectively.
2. The tumor must be of a type known to respond poorly to standard radiation therapy.
3. The patient must be willing to accept experimental therapy and be likely to survive the four to six weeks required for treatment and evaluation.

The total number included in the study was 25. The population at the hospital where this study was conducted is such that epidermoid carcinomas of the lung and larynx constitute the majority of tumors meeting the above criteria. In these two types of malignant lesions, 5-fluoro-uracil alone has proven ineffective.

The following studies were performed on every patient: Leukocyte count and determination of cell differential, hemoglobin content and platelet count three times a week; reticulocyte count, urinalysis, and determination of serum albumin, globulin, uric acid and alkaline phosphatase once weekly. The patients were examined daily for evidence of toxicity. The response of the malignant lesion to combined therapy was measured at the end of treatment and every two weeks thereafter.

TOXICITY

Toxic effects observed in this study were mild esophagitis in four patients, moderately severe pharyngitis in three and severe proctitis in one patient. In each such case the area of inflammation was within the field of radiation.

Leukopenia (less than 3,000 per cu. mm.) occurred in four patients, the number rapidly returning to normal range upon completion of therapy. Thrombocytopenia (less than 100,000 per cu. mm.) occurred in four patients, the lowest count being 55,000 per cu. mm. The thrombocytopenia was not manifest clinically.

In 13 patients, no toxic effects were noted. Not observed in this study were nausea and vomiting, gastrointestinal hemorrhage, shock, pneumonia or death. In no case did anemia or hepatic or renal toxicity occur. Two patients, each of whom received

TABLE 1.—*Results of Combined 5-Fluoro-uracil and Roentgen Therapy of Malignant Disease*

Diagnosis	Total Treated	Response			Not Evaluable
		Good	Moderate	None	
Carcinoma of lung	8	8	....	....	....
Carcinoma of larynx	3	1	1	1	....
Adenocarcinoma of rectum	2	1	....	1	....
Adenocarcinoma of stomach	1	1	....	....	....
Carcinoma of esophagus	2	....	....	1	1
Embryonal cell cancer of testis	1	1	....	....	....
Transitional cancer of bladder	1	....	....	....	1
Lymphoepithelioma	1	....	....	....	1
Carcinoma of pancreas	1	....	....	....	1
Carcinoma of tonsil	1	....	1	....	....
Clear cell cancer of kidney	1	....	....	....	1
Malignant melanoma	1	....	....	....	1
Carcinoma of scalp	1	....	1	....	....
Adenocarcinoma of lung	1	....	....	....	1
Total	25	12	3	3	7

two complete courses of combined therapy in a period of two months, experienced no toxicity of any kind.

RESULTS

Of eight patients with epidermoid carcinoma of the lung (a kind of tumor that had shown no response to 5-fluoro-uracil alone in other reported studies) all showed rapid and significant regression of the lesions receiving x-ray therapy during 5-fluoro-uracil administration. Several were in good health without evidence of tumor six months after therapy. Similar responses were observed in single cases of epidermoid carcinoma of the larynx, adenocarcinoma of the rectum, mucinous adenocarcinoma of the stomach and embryonal cell carcinoma of the testis.

One patient each with epidermoid carcinoma of the larynx, epidermoid carcinoma of the esophagus and adenocarcinoma of the rectum showed no objective improvement.

The remaining ten patients had either a moderately favorable response (slight tumor regression with symptomatic improvement) or could not be evaluated with respect to tumor response.

The patient with embryonal cell carcinoma of the testis had two large metastatic lesions in the lungs, one of which was treated with 5-fluoro-uracil plus x-ray, the other with x-ray alone. X-ray films of the chest showed no response of the lesions to 5-fluoro-uracil alone, slight regression when treated with 2,000 r. alone, and complete disappearance with the simultaneous use of both forms of therapy. (See Figure 1.)

CONCLUSION

The concurrent administration of 5-fluoro-uracil and local radiation produced a greater degree and higher incidence of tumor regression than has been reported with either mode of therapy given alone. The effects observed in this study also exceeded those expected on the basis of adding together the separate responses obtainable by either mode of therapy. Thus, true antitumor synergism appears to exist in this form of combined therapy. More extensive study of this method of cancer therapy is indicated.

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ADDENDUM: In a separate study, conducted by one of the authors (B.H.) an additional 75 patients with malignant disease have been treated with varying doses of 5-fluoro-uracil and x-irradiation. The results in this study have been similar to those reported here.

REFERENCES

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When to Operate?

"One should operate only when there are several chances of success; to operate without a chance, means to prostitute the exalted art and science of surgery, and make it dubious in the minds of the laity and colleagues. But where is the measure according to which the chance of success can be gauged? It lies in the untiring study of our science, in the acute criticism of our own observation as well as the observation of others, in the minutest examination of each case and in the critical evaluation of our experiences."—*Theodor Billroth (1829-94).*

From Briefe von Theodor Billroth, ed. by Fischer, 1895